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Impact of Age on Coronary Artery Plaque Progression: PARADIGM substudy

Brief Title: Age and coronary artery plaque progression

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ABSTRACT

Background: The association of age with coronary plaque dynamics is not well characterized.

Objectives: To analyze the effect of age on the progression of whole-heart coronary plaque in patients who underwent serial coronary computed tomography angiography (CCTA).

Methods: From a multinational registry of patients who underwent serial CCTA, 1,153 subjects (61±5 years old, 61.1% male) aged 40~75 years old with at least one detectable plaque were analyzed. Annualized volume changes of total, fibrous, fibrofatty, necrotic core, and dense calcification plaque components of the whole heart were compared by age quartile groups. Random forest analysis was used to define the relative importance of age on plaque volume progression.

Results: The median interval between the two CCTA was 3.3 (interquartile range 2.6~4.8) years. The median annual volume changes of total plaque in each age quartile group was 7.8, 10.5, 10.8, and 12.1mm^3/year and for dense calcification, 2.5, 4.6, 5.4, and 7.1mm^3/year, both of which demonstrated a tendency to increase by age (p-for-trend=0.001 and <0.001, respectively). However, this tendency was not observed in the fibrous, fibrofatty, and necrotic core components. In the propensity score-matched population (n=318 per group), the annual change of total plaque volume (7.8 vs 11.5 mm^3/year, p=0.008) and the dense calcification component (2.5 vs. 5.9 mm^3/year, p<0.001) was significantly smaller in the lowest age quartile group versus the other age groups. Random forest analysis demonstrated that, apart from the baseline total plaque volume, age had a comparable importance in the total plaque volume progression as other traditional factors such as the serum lipid, sugar level and renal function.

Conclusions: The rate of annual plaque progression increases gradually depending on age, which is a result of the growth of dense calcification. Age is a significant factor in the plaque growth, the importance of which is comparable to other traditional risk factors.

KEYWORDS: coronary artery disease; computed tomography; aging; atherosclerotic plaque; disease progression.

CONDENSED ABSTRACT

The association of age with the coronary plaque dynamics is not known enough. In this analysis of the whole-heart coronary plaques from a multinational registry of patients who underwent serial CCTA, the annualized total plaque volume tended to increase significantly by age. This was mainly a result of the growth of dense calcification component than any other plaque components. By random forest analysis, apart from the baseline total plaque volume, age had a comparable importance in the total plaque volume progression as other traditional cardiovascular factors

such as the serum lipid, sugar level and renal function.

ABBREVIATIONS LIST

CAD = coronary artery disease
CACS = coronary artery calcium score
CCTA = coronary computed tomography angiography
CVD = cardiovascular disease
HU = Hounsfield units
IVUS = intravascular ultrasound
IQR = interquartile range
OCT = optical coherence tomography
ROC = receiver operating characteristic

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in developed countries, and coronary atherosclerosis accounts for the most substantial proportion of CVD (1). Because age and dyslipidemia are important risk factors for coronary artery disease (CAD), several guidelines recommend the consideration of using lipid-lowering agents by age groups (2,3) and mainly, focuses on middle-aged groups, i.e. 40~75 years old.

Age is a well-known major risk factor of CVD, which stems out from numerous results of multivariate analysis in a vast number of papers. However, only a few papers have focused on age itself as the central factor of CVD and moreover, the relationship between age and coronary atherosclerosis has not been addressed properly (4,5). Prior papers that report a serial follow-up of coronary plaque progression have been mainly based on quantitative coronary angiography, intravascular ultrasound (IVUS) or optical coherence tomography (OCT) (6,7), all of which carry an inherent limitation of selection bias for high-risk patients owing to the invasiveness of the methods used. Therefore, coronary CT angiography (CCTA) is an adequate noninvasive modality to analyze the progression of coronary plaque according to age in low-to-intermediate CAD risk population, as compared to invasive modalities such as IVUS (8). Importantly, the use of noninvasive imaging to analyze the progression of CAD is very useful because it sheds light to understanding the natural history of CAD in the general population.

In this study, we postulated that it would be possible to analyze the effect of age on the progression of coronary plaque with a sufficiently large population who underwent serial CCTA. The objective of this study is two-fold; first, we tried to analyze the rate of coronary plaque growth in relation to age, and second, we aimed to investigate the relative importance of age on coronary plaque growth in relation to other traditional CVD risk factors.

Methods

Study subjects and protocol

The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) registry is an international, prospective, open-label, multicenter observational registry that collected clinical and outcome data of patients who underwent serial CCTA (9). In brief, data was collected from 2,252 subjects who underwent clinically indicated serial CCTA at 13 sites in 7 countries between 2003 and 2015. All subjects who were enrolled in PARADIGM registry underwent longitudinal CCTA using 64-rows or greater scanners with at least a 2-year interscan interval. Patients with at least one quantitatively non-interpretable CCTA (n=492), no visible plaque on both baseline and follow-up CCTA (n=262), previously revascularization treatment, whether percutaneous coronary intervention or coronary artery bypass graft (n=248), were excluded from this analysis.

Because we wanted to concentrate the analysis to the middle-age group, the group of patients who are the main target of primary prevention in the guidelines (2), those below 40-years old (n=15) and over 75-year old (n=104) at enrollment were also excluded. Finally, 1,153 subjects were the target population of analysis in this study (**Figure 1**). These subjects were classified into quartiles according to the age at the time of initial CCTA, with the 1st quartile defined as the youngest population and the 4th quartile the oldest. We used standardized definitions for the cardiovascular risk factor (9). Our study data including

demographics, medical history, laboratory data and the occurrence of clinical events were collected prospectively within one month from the initial and subsequent CCTA (9). The study was approved by the institutional review boards of all participating centers.

CCTA protocol and the image analysis

All CCTA scans were done in accordance with the Society of Cardiovascular Computed Tomography guidelines (10,11). All CCTA datasets from participating centers were transferred to the core laboratory for blinded image analysis. Coronary atherosclerotic plaque analysis was performed by level III experienced reader using semi-automated software (QAngioCT Research Edition v2.1.9.1; Medis Medical Imaging Systems, Leiden, the Netherlands) with manual correction (8). All coronary artery segments with a diameter ≥2mm were analyzed using a modified 17-segment American Heart Association model (11). Atherosclerosis on CCTA was defined as any tissue ≥1mm^2 within or adjacent to the lumen identified in >2 planes that could be differentiated from the surrounding intrathoracic tissue such as the epicardial fat or the pericardium (11). Plaque volumes (mm^3) of all coronary segments were acquired and then summated to create the total plaque volume on the per-patient level. The annual change of plaque volume was defined as the difference between baseline and follow-up plaque volume divided by the time interval between the serial CT studies. The atherosclerotic plaque was further subclassified by composition, using pre-defined intensity cutoff values in

Hounsfield units (HU) for necrotic core (-30 to 30HU), fibrofatty (31 to 130HU), fibrous (131 to 350HU), and dense calcification (≥351HU) components (12,13). The mean plaque burden was calculated as follows: [(the plaque volume of the entire vessels / the entire vessel volume) x100] (%).

Study endpoint

The primary endpoint of the current study is the annual change of the total plaque volume and each plaque component volume between the serial CCTAs. The rate of plaque volume and each component changes were compared between each age quartile groups.

Statistical analysis

Continuous variables are presented as mean±standard deviation or median [interquartile range (IQR)], depending on whether normality is satisfied by the Shapiro-Wilk test. Categorical variables are shown as absolute counts (percentage). The comparison of categorical variables was done using a Chi-square test or Fisher's exact test and that of the continuous variables using Student's t-test or Mann-Whitney U-test, as appropriate. The trend of the change in plaque volume according to age groups was analyzed by the Cochran–Armitage test. To reduce the effect of the difference in baseline characteristics other than the age, we adjusted for differences in baseline characteristics of patients using propensity score matching with the greedy nearest matching technique

(14). All variables of absolute standardized mean difference ≥0.1, including the statin medication, were used for propensity score matching analysis (**Supplementary Table 1**) and the subjects from the 2^{nd}~4^{th} age quartile groups were 1:1 matched to those in the 1^{st} age quartile group.

Random forest analysis (15) was used to identify the importance of age in the rapid progression of total plaque progression, defined as the total plaque volume progression larger than the median value. We divided the total population into the derivation (65%) and the validation population (35%). Random forest analysis was done with 5-fold internal cross-validation with the data from the derivation population. We validated the optimized model created from the derivation cohort using the receiver operating characteristic (ROC) analysis in the validation cohort. The importance of each variables in the random forest analysis was calculated using the classification error for the random forest trees and the error after permuting the predictor variables (15). All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 20.0 (IBM Co., Armonk, NY, USA) or R version 3.6.0 software (R Development Core Team, Vienna, Austria), and a two-tailed p-value <0.05 was considered significant for all analysis.

Results

Baseline demographic characteristics of the study participants

Among the 1,153 patients (mean age, 60.4±7.7 years), 61% (n=705) were male. There were 255 diabetes patients (22%). The participants were classified into quartiles according to age at the initial CCTA; Q1, 40~55 years old; Q2, 56~61; Q3, 62~66; and Q4, 67~75 (**Supplementary Figure 1**). The baseline clinical characteristics are compared between the four age groups (**Table 1**). The lowest age quartile group (Q1) had a higher proportion of males, current smoker but lower systolic blood pressure and the prevalence of traditional cardiovascular risk factors in general. The proportion of patients taking antiplatelet agents or antihypertensives was also the lowest in the lowest age quartile group. The same group had a higher glomerular filtration rate and total cholesterol, triglyceride, and low density lipoprotein-cholesterol.

Baseline plaque volume and its changes according to age

The median interval between the two CCTA examinations was 3.3 years (IQR 2.6 to 4.8 years). There was no difference in the time interval between the two CCTA examinations between the four age quartile groups (**Table 1**).

At the initial CCTA examination, the median total plaque volume was 65.2mm^3/year (IQR 22.0~160.6) and the median mean plaque burden 3.0% (IQR 1.1~7.5) in the entire population. The total plaque volume, as well as the fibrous and dense calcification component volume and the

mean plaque burden at baseline was the lowest in the lowest age quartile group. There was a significant trend towards an increase of the above parameters across the age quartile groups (all p-for-trend=0.001) (**Table 2**). However, the fibrofatty and the necrotic core component volume did not differ between the age quartile groups nor were there trends across the age groups (**Supplementary Figure 2**).

As for the annual change of the coronary plaques, the median total plaque volume change per year was 10.0mm^3/year (IQR 3.6~23.2) in the entire population. The annual change of the total plaque, dense calcified component volume, and the mean plaque burden were the lowest in the lowest age quartile group. The same parameters demonstrated a significant trend towards an increase across the age quartile groups (all p-for-trend<0.001; **Figure 2**). However, there was no significant association of age with the change of fibrous, fibrofatty and necrotic core components across the four age quartile groups.

Baseline plaque volume and its changes in the propensity score-matched population

To analyze the sole effect of age on coronary plaques, we adjusted for differences in baseline characteristics using the propensity score matching. The propensity matching results were satisfactory, with no difference in any baseline characteristics other than age (**Supplementary Table 1**).

The annual change of total plaque, dense calcification component

volume, and the mean plaque burden was significantly lower in the lowest age quartile group compared with the other age quartile groups. This trend did not change after propensity score matching (**Table 3**, **Figure 3**). However, there was no significant difference in the change of fibrous, fibrofatty and necrotic core components between the lowest age quartile group versus the other age quartile groups.

Relative importance of age in coronary plaque progression in comparison with other cardiovascular risk factors

Using random forest analysis, we analyzed how important age would be in predicting the rapid coronary plaque progressors, defined as those with the total plaque volume progression larger than the median value, in relation to other cardiovascular risk factors. The best predictive random forest model using the derivation cohort was built on a model of ntree 2000, with an area under the curve of 0.75 (95% confidence interval 0.70 to 0.79) when tested on the validation dataset.

Apart from the baseline total plaque volume, which was the most crucial factor in predicting the rapid progressors, age was as crucial as other cardiovascular risk factors, such as body mass index, serum glucose, and serum lipid level (**Figure 4**). More specifically, assuming that the importance of baseline total plaque volume is 100, the relative importance of age at the initial CCTA examination was 27. The relative importance of most of the traditional cardiovascular risk factors ranged from 23 to 29, which were similar with that of age (**Supplementary**

Table 2).

Discussion

The present study of a large cohort of patients who underwent two serial CCTAs demonstrated that age is significantly associated with the growth of coronary plaque burden in the whole heart. This trend in the increase of coronary atherosclerosis by age is largely and significantly driven by the increase in the amount of calcified plaque. Although the baseline degree of coronary atherosclerosis is the sole important factor associated with the growth of coronary plaque, age was as important as any other traditional cardiovascular risk factors. These findings demonstrate that the contribution of age to coronary atherosclerosis is not because of the comorbidities associated with aging but age itself as a significant risk factor.

The association between age and rate of total plaque volume progression

Annual changes of the total plaque volume in the serial CCTAs of the present study were different between the age quartile groups, and the lowest quartile had a significantly slower progression rate than the other age groups. A recent analysis done with the CCTA suggested that age predicts future major adverse cardiovascular events (4). The present study is the first large prospective multi-ethnic observational registry to identify that the rate of plaque progression on CCTA increases with age, demonstrating a possible mechanism of the previous study.

Atherosclerosis is a dynamic process with chronic inflammation as

the most critical molecular and cellular mechanism (16). Persistent hypercholesterolemia in isolation does not cause atherosclerosis, but the age-associated exhaustion of the progenitor cells is a determinant of atherosclerosis in animal models (17). Recently, clonal hematopoiesis of indeterminate potential (CHIP), a clonal expansion of hematopoietic stem cells, has been shown to be a predictor of various cardiovascular diseases (18). The prevalence of CHIP is associated with aging, and the function of progenitor cells is bound to decline with age (19). These previous findings may provide a plausible cellular mechanism of why aging itself is associated with the progression of coronary atherosclerosis in our analysis.

Age and calcified plaque volume progression – the mechanism and clinical significance

Calcified plaque refers to the progression of microscopic calcium deposition in the atherosclerotic plaque to more massive sheets or plates that could be detected macroscopically (20). There are several complex inhibitory mechanisms against the formation of calcified plaque in the baseline atherosclerotic lesion (20-23). The plasma level of Klotho, which is a protein that inhibits vascular calcification by decreasing the expression of phosphate transporter 1 (PiT1) in the vascular smooth muscle cell membrane, declines with age (23). Matrix Gla protein (MGP), a member of the family of vitamin-K2 dependent protein, is a potent inhibitor of vascular calcification, the inactive form of which increases with

age and is a significant predictor of vascular calcification (24). These suggest that there are various anti-calcific molecular mechanisms that decreases with age and that the increase of calcified plaque in the older age groups may be explained by the failure of these anti-calcific molecular mechanisms.

The coronary artery calcium score (CACS) has been used for risk stratification in the primary prevention of CVD because it predicts future major adverse cardiovascular events in patients at intermediate risk (2,25). The progression of CACS demonstrates an exponential increase with age in the middle age group with no history of CAD (26). In a previous study, the increase in CACS showed a statistically significant positive correlation with the increase in the total and calcified plaque (27). Our findings emphasizes these previous findings that the increase in the calcified plaque component by age is significantly associated with the increase in the total coronary atheroma burden of the whole heart. Based on our analysis, patients with a more advanced age would be expected to have a more rapid progression of total and calcified plaque than that of the younger patients with a similar value of CACS at baseline.

Relative importance of age in coronary plaque progression

Several algorithms have been designed to interprete traditional risk factors for CVD and to provide individual risk scores, where age has always been included in risk evaluation for CVD (2,28,29). Keeping all other variables constant, increase of the age elevates the risk of CVD

abruptly in these algorisms (5). With the random forest analysis in our study, we could also specify that age was an essential factor in rapid plaque progression along with, and indepently of other traditional cardiovascular risk factors.

Aging is a complex process that is associated with various changes in the homeostatic mechanism of the body. Therefore, it is very difficult to analyze the effect of age in isolation. Some investigators have emphasized that age may be a ‘modifiable’ risk factor for CVD (30), which stems from the fact that the prevalence of comorbidities/risk factors increases with age and that age reflects the time-related exposure to numerous cardiovascular risk factors. However, a recent study of Tsimane subjects with very few cardiovascular risk factors have also pointed to the significant association of age with CACS (31). The association of age with atherosclerosis has also been demonstrated in the preindustrial population as well (32). These findings indicate that we do not completely understand the effect of age on coronary plaque progression but directs us to future research in understanding the association of age with potential modifiable situations. For example, the age-associated decrease in the antioxidant effect may be a potential mechanism and a possible therapeutic option that should be pursued in the future (33).

Limitation

Our study has some limitations. First, since this is an observational registry designed to investigate the natural course of the low-intermediate

risk population of coronary artery atherosclerosis, a possible selection bias could not be avoided, and therefore, the difference in annual changes of plaque volume in high-risk acute coronary syndrome patients could not be demonstrated. Second, statin might be a confounding factor that mediates the association between age and calcified plaque progression. A recent study suggests that statin use is associated with a higher rate of calcified plaque volume progression (27), and the elderly patients were more likely to take statins. However, we demonstrated that the older age group still has a higher plaque progression rate even after rigorous propensity score matching. This means that age is an independent risk factor for calcified plaque progression, regardless of the statin use.

Conclusion

The rate of annual coronary plaque volume progression increases significantly with age. The dense calcification plaque component is the main component that explains the growth of coronary plaques by age. The mechanism of why age is a significant predictor of coronary plaque progression warrants further investigations in the future.

PERSPECTIVES

Clinical Competencies: Age is a significant risk factor of incident cardiovascular disease. Using CCTA for the quantitative plaque analysis of the whole heart, age was significantly associated with coronary plaque growth, the relative importance of which is comparable to other traditional cardiovascular risk factors such as serum sugar or lipid level.

Translational Outlook: Although the age-associated progression of coronary atherosclerosis may be explained partially by a longer term exposure to cardiovascular risk factors, further studies are needed to identify the mechanism of why age is related to the progression of coronary atherosclerosis, which may lead us to the development of novel therapeutics.

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Figure legend

Central illustration. Comparison of coronary plaque progression between the older and younger subjects on serial coronary computed tomography angiography images.

(A) A 69-year-old subject with significant changes of the total plaque volume (38.4mm^3/year). (B) A 54-year-old subject with minimal changes of the total plaque volume (5.3mm^3/year). (C) Significant trend in the increase of annualized coronary plaque volume progression by age.

Figure 1. Flow chart of the study participants.

CCTA, coronary computed tomography angiography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Figure 2. Annualized change rate of whole-heart coronary plaque and its components between the serial CCTAs according to age quartile groups.

Values are presented as median+standard error. (**A**) Annual change of total plaque volume per patient (mm^3/year). (**B**) Annual change of fibrous plaque volume (mm^3/year). (**C**) Annual change of calcified plaque volume (mm^3/year). (**D**) Annual change of mean plaque burden (%/year). CCTA, coronary computed tomography angiography. Q1 (quartile 1), 40~55; Q2 (quartile 2), 55~61; Q3 (quartile 3), 61~66; Q4 (quartile 4), 66~75 years old.

Figure 3. Annualized change rate of whole-heart coronary plaque and its components between the serial CCTAs in the propensity score matched cohort.

The entire population was 1:1 matched between the 1st age quartile group versus the 2nd~4th quartile groups. Values are presented as median+standard error. (**A**) Annual change of total plaque volume per patient (mm^3/year). (**B**) Annual change of fibrous plaque volume (mm^3/year). (**C**) Annual change of calcified plaque volume (mm^3/year). (**D**) Annual change of mean plaque burden (%/year). CCTA, coronary computed tomography angiography. Q1 (quartile 1), 40~55; Q2 (quartile 2), 55~61; Q3 (quartile 3), 61~66; Q4 (quartile 4), 66~75 years old.

Figure 4. Random forest analysis results for the analysis of relative variable importance in predicting rapid plaque progressors.

Among the 31 variables, only the top 20 important variables are shown. The importance of the most significant variable, baseline total plaque volume, was set as 100 and the relative importance of each variables were compared. LDL, low-density lipoprotein; GFR (CKD-EPI), glomerular filtration rate (chronic kidney disease – epidemiology collaboration); TG, triglyceride; HDL, high-density lipoprotein; BMI, body mass index; CT, computed tomography; SLNG, sublingual nitroglycerin; CVD, cardiovascular disease.

Table 1. Baseline characteristics comparison between the age quartile groups at the time of baseline CCTA.

	Entire population (N=1,153)	Quartile 1 (N=318)	Quartile 2 (N=279)	Quartile 3 (N=271)	Quartile 4 (N=285)	p-value
Age, years	60.4 ± 7.7	50.4 ± 3.9	58.7 ± 1.7	64.0 ± 1.4	69.8 ± 2.2	<0.001
Male, n (%)	705 (61.1%)	225 (70.8%)	172 (61.6%)	163 (60.1%)	145 (50.9%)	<0.001
Ethnicity						0.412
African	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	
Caucasian	315 (27.3%)	77 (24.2%)	71 (25.4%)	77 (28.4%)	90 (31.6%)	
East Asian	795 (69.0%)	232 (73.0%)	195 (69.9%)	183 (67.5%)	185 (64.9%)	
Latin American	41 (3.6%)	9 (2.8%)	12 (4.3%)	11 (4.1%)	9 (3.2%)	
South Asian	1 (0.1%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	
BMI, kg/m^2	25.5 ± 3.2	25.8 ± 3.1	25.8 ± 3.3	25.2 ± 3.1	25.2 ± 3.4	0.030
SBP, mmHg	130.2 ± 16.3	127.3 ± 16.2	130.1 ± 15.2	131.4 ± 16.6	132.3 ± 16.9	<0.001
DBP, mmHg	78.7 ± 9.9	79.6 ± 10.6	78.9 ± 9.9	79.0 ± 9.2	77.3 ± 9.6	0.018
Cardiovascular risk factors, n (%)						
Hypertension	632 (54.8%)	134 (42.1%)	153 (54.8%)	163 (60.1%)	182 (63.9%)	<0.001
Diabetes mellitus	255 (22.1%)	54 (17.0%)	68 (24.4%)	62 (22.9%)	71 (24.9%)	0.069
Dyslipidemia	485 (42.1%)	128 (40.3%)	121 (43.4%)	117 (43.2%)	119 (41.8%)	0.856
Atrial fibrillation	67 (5.8%)	11 (3.5%)	14 (5.0%)	14 (5.2%)	28 (9.8%)	0.007
Familial history of CAD	326 (28.3%)	101 (31.8%)	81 (29.0%)	72 (26.6%)	72 (25.3%)	0.302
Stroke	58 (5.0%)	5 (1.6%)	12 (4.3%)	19 (7.0%)	22 (7.7%)	0.00

	Entire population (N=1,153)	Quartile 1 (N=318)	Quartile 2 (N=279)	Quartile 3 (N=271)	Quartile 4 (N=285)	p-value
						2
Current smoker	221 (19.2%)	85 (26.7%)	61 (21.9%)	42 (15.5%)	33 (11.6%)	<0.001
Medication history, n (%)						
Antiplatelet agents	483 (41.9%)	97 (30.5%)	126 (45.2%)	124 (45.8%)	136 (47.7%)	<0.001
RAS blockade	348 (30.2%)	80 (25.2%)	85 (30.5%)	97 (35.8%)	86 (30.2%)	0.049
Beta blocker	327 (28.4%)	71 (22.3%)	63 (22.6%)	83 (30.6%)	110 (38.6%)	<0.001
CCB	263 (22.8%)	52 (16.4%)	61 (21.9%)	68 (25.1%)	82 (28.8%)	0.003
Diuretics	103 (8.9%)	19 (6.0%)	21 (7.5%)	26 (9.6%)	37 (13.0%)	0.019
Nitrate	95 (8.2%)	17 (5.3%)	25 (9.0%)	24 (8.9%)	29 (10.2%)	0.154
Statins	543 (47.1%)	127 (39.9%)	128 (45.9%)	133 (49.1%)	155 (54.4%)	0.004
Oral hypoglycemics	112 (9.7%)	26 (8.2%)	22 (7.9%)	33 (12.2%)	31 (10.9%)	0.237
Laboratory findings						
GFR, mL/min/1.73m^2	78.7 [67.8–89.3]	84.4 [74.1–96.6]	81.7 [70.7–93.6]	77.5 [64.7–88.6]	74.3 [65.0–83.5]	<0.001
Glucose, mg/dL	101.0 [94.0–111.0]	101.0 [94.0–110.0]	101.0 [94.8–112.0]	100.4 [94.0–111.0]	101.0 [94.0–109.0]	0.970
Total cholesterol, mg/dL	187.0 [167.0–213.0]	192.0 [174.0–220.0]	185.0 [164.0–209.3]	188.0 [165.0–213.0]	182.0 [166.0–210.0]	0.001
HDL cholesterol, mg/dL	49.0 [42.0–57.0]	47.0 [42.0–56.0]	48.5 [41.0–55.9]	49.9 [43.0–57.5]	49.5 [42.0–58.0]	0.158
Triglyceride, mg/dL	134.0 [96.0–176.0]	149.9 [97.0–199.3]	130.0 [95.0–171.5]	131.0 [95.5–171.6]	125.0 [95.0–157.0]	<0.001

	Entire population (N=1,153)	Quartile 1 (N=318)	Quartile 2 (N=279)	Quartile 3 (N=271)	Quartile 4 (N=285)	p-value
LDL cholesterol, mg/dL	113.0 [93.5–136.0]	119.0 [99.4–142.0]	111.0 [92.0–133.0]	115.0 [93.0–136.0]	110.5 [92.6–132.0]	0.002
CCTA interval	3.8 ± 1.6	3.9 ± 1.7	3.7 ± 1.4	3.9 ± 1.7	3.8 ± 1.5	0.655

Categorical variables are presented as the number (percent). Continuous variables are presented as mean±standard deviation or median [interquartile range], as appropriate. The age group was classified by quartiles, Quartile 1, 40~55 years old; Quartile 2, 55~61; Quartile 3, 61~66; Quartile 4, 66~75. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; RAS, renin-angiotensin system; CCB, calcium channel blocker; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CCTA, Coronary computed tomography angiography.

Table 2. Baseline and annual changes of the whole-heart coronary plaque and its components between the serial CCTAs.

	Entire population (N=1,153)	Quartile 1 (N=318)	Quartile 2 (N=279)	Quartile 3 (N=271)	Quartile 4 (N=285)	p for trend
Baseline CCTA analysis of the whole-heart coronary plaques						
Total plaque volume (mm^3)	65.2 [22.0–160.6]	49.4 [10.5–128.0]	65.6 [21.8–153.8]	70.4 [24.7–150.6]	82.4 [28.8–198.8]	<0.001
Fibrous component volume (mm^3)	28.6 [9.7–67.0]	21.7 [6.2–52.1]	31.0 [9.7–66.6]	29.6 [10.8–70.1]	31.9 [12.7–83.6]	0.001
Fibrofatty component volume (mm^3)	6.9 [0.5–26.5]	7.5 [0.2–31.7]	7.9 [0.4–29.6]	6.0 [0.5–23.2]	6.1 [0.8–23.1]	0.094
Necrotic core component volume (mm^3)	0.1 [0.0–1.8]	0.1 [0.0–2.3]	0.2 [0.0–2.1]	0.1 [0.0–1.1]	0.1 [0.0–1.8]	0.132
Dense calcification component volume (mm^3)	12.4 [1.0–43.8]	3.2 [0.0–23.7]	12.9 [1.4–36.6]	17.3 [2.5–51.1]	26.8 [6.2–75.3]	<0.001
Fibrofatty + necrotic core component volume (mm^3)	7.2 [0.5–30.5]	7.9 [0.2–34.7]	8.1 [0.4–34.8]	6.2 [0.6–26.4]	6.2 [0.8–26.9]	0.087
Non-calcified component volume (mm^3)	40.8 [11.8–108.9]	35.2 [8.1–93.6]	42.5 [11.4–108.6]	42.8 [17.2–102.7]	45.9 [15.1–118.5]	0.117
Mean plaque burden (%)	3.0 [1.1–7.5]	2.1 [0.6–5.5]	3.1 [1.1–7.5]	3.4 [1.3–6.8]	4.9 [1.4–10.3]	<0.001
Annual changes of the whole-heart plaque volume and its components						
Total plaque volume (mm^3/year)	10.0 [3.6–23.2]	7.8 [3.0–18.5]	10.4 [3.7–23.9]	10.8 [4.3–24.2]	12.1 [4.4–28.1]	0.001
Fibrous component volume (mm^3/year)	3.0 [0.0–9.5]	3.0 [0.6–8.1]	4.3 [0.6–11.2]	2.6 [-0.7–9.4]	2.8 [-0.7–9.9]	0.363
Fibrofatty component volume (mm^3/year)	0.0 [-1.2–2.1]	0.0 [-1.6–2.1]	0.1 [-1.0–2.2]	0.0 [-1.2–1.8]	0.0 [-0.8– 2.1]	0.617
Necrotic core	0.0 [-	0.0 [0.0–	0.0 [-	0.0 [0.0–	0.0 [0.0–	0.44

	Entire population (N=1,153)	Quartile 1 (N=318)	Quartile 2 (N=279)	Quartile 3 (N=271)	Quartile 4 (N=285)	p for trend
component volume (mm^3/year)	0.1–0.1]	0.2]	0.1–0.1]	0.1]	0.1]	4
Dense calcification component volume (mm^3/year)	4.7 [1.2–13.0]	2.5 [0.6–8.1]	4.6 [1.0–11.6]	5.4 [1.7–14.9]	7.1 [2.6–19.0]	<0.001
Fibrofatty + necrotic core component volume (mm^3/year)	0.0 [-1.2–2.3]	0.0 [-1.7–2.4]	0.1 [-1.2–2.3]	0.0 [-1.2–1.7]	0.0 [-1.0–2.3]	0.774
Non-calcified component volume (mm^3/year)	3.1 [-0.8–11.2]	3.1 [-0.3–9.5]	4.2 [0.1–13.2]	1.4 [-2.3–10.6]	3.1 [-1.0–12.1]	0.406
Mean plaque burden (%/year)	0.5 [0.2–1.1]	0.3 [0.1–0.9]	0.5 [0.2–1.3]	0.5 [0.2–1.1]	0.6 [0.2–1.3]	<0.001

Variables are presented as median [interquartile range]. Age group was classified by 4 quartiles, Quartile 1, 40~55 years old; Quartile 2, 55~61; Quartile 3, 61~66; Quartile 4, 66~75. CCTA, coronary computed tomography angiography.

	Crude population			Propensity-matched population		
	Quartile 1 (N=318)	Quartiles 2~4 (N=835)	p-value	Quartile 1 (N=318)	Quartiles 2~4 (N=318)	p-value
Baseline CCTA analysis						
Total plaque volume (mm^3)	49.4 [10.5–128.0]	73.2 [26.0–169.1]	<0.001	49.4 [10.5–128.0]	71.1 [23.1–160.6]	0.003
Fibrous component volume (mm^3)	21.7 [6.2–52.1]	30.6 [11.3–73.4]	<0.000	21.7 [6.2–52.1]	29.1 [10.0–65.9]	0.011
Fibrofatty component volume (mm^3)	7.5 [0.2–31.7]	6.6 [0.5–25.5]	0.725	7.5 [0.2–31.7]	5.4 [0.4–22.4]	0.446
Necrotic core component volume (mm^3)	0.1 [0.0– 2.3]	0.1 [0.0–1.7]	0.905	0.1 [0.0– 2.3]	0.1 [0.0–1.7]	0.688
Dense calcification component volume (mm^3)	3.2 [0.0–23.7]	17.3 [2.6–52.8]	<0.001	3.2 [0.0–23.7]	16.4 [1.6–49.2]	<0.001
Fibrofatty + necrotic core component volume (mm^3)	7.9 [0.2–34.7]	6.8 [0.6–27.8]	0.703	7.9 [0.2–34.7]	5.6 [0.4–26.2]	0.450
Non-calcified component volume (mm^3)	35.2 [8.1–93.6]	43.5 [14.8–111.1]	0.019	35.2 [8.1–93.6]	38.4 [12.1–117.2]	0.171
Mean plaque burden (%)	2.1 [0.6–5.5]	3.7 [1.2– 8.4]	<0.001	2.1 [0.6– 5.5]	3.4 [1.1– 8.4]	<0.001
Annual changes of plaque						
Total plaque volume (mm^3/year)	7.8 [3.0–18.5]	11.1 [4.1–25.1]	0.001	7.8 [3.0–18.5]	10.7 [3.8–25.7]	0.014
Fibrous component volume (mm^3/year)	3.0 [0.6–8.1]	3.1 [-0.3–10.0]	0.557	3.0 [0.6–8.1]	3.0 [-0.3–10.0]	0.771
Fibrofatty component volume (mm^3/year)	0.0 [-1.6–2.1]	0.0 [-1.0–2.1]	0.978	0.0 [-1.6–2.1]	0.0 [-1.1–1.7]	0.781
Necrotic core component volume (mm^3/year)	0.0 [-0.0–0.2]	0.0 [-0.1–0.1]	0.229	0.0 [-0.0–0.2]	0.0 [-0.1–0.1]	0.051
Dense calcification component volume (mm^3/year)	2.5 [0.6–8.1]	5.9 [1.6–15.1]	<0.001	2.5 [0.6–8.1]	6.0 [1.3–15.1]	<0.001
Fibrofatty + necrotic core component volume (mm^3/year)	0.0 [-1.7–2.4]	0.0 [-1.2–2.3]	0.792	0.0 [-1.7–2.4]	0.0 [-1.2–1.8]	0.571
Non-calcified component volume (mm^3/year)	3.1 [-0.3–9.5]	3.1 [-0.9–12.2]	0.573	3.1 [-0.3–9.5]	2.8 [-0.7–12.3]	0.622

Mean plaque burden (%/year)	0.3 [0.1–0.9]	0.6 [0.2–1.2]	<0.001	0.3 [0.1–0.9]	0.5 [0.2–1.3]	0.001

Table 3. Changes of whole-heart coronary plaque and its components plaque between the lowest age quartile and the other age groups.

Variables are presented as median [interquartile range]. Age group was classified by 4 quartiles, Quartile 1, 40~55 years old; Quartile 2, 55~61; Quartile 3, 61~66; Quartile 4, 66~75. CCTA, coronary computed tomography angiography.